Docket No. 2006D-0331
Conduct of Emergency Research; Public Hearing
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I am an interested party who submitted a public comment to the docket for the interim final rule in 1996, have followed the uses of emergency research since then, and have worked intensively over the last 2 years to foster public discussion about the PolyHeme trial and the application of the emergency consent waiver rule in that trial.

Responses to FDA Questions (I have not responded to every question):

(1) Are the 50.24 criteria adequate?

I do not consider the 50.24 criteria inadequate per se. However, it is quite clear that in practice they are regarded as inadequate by many sponsors, investigators, and IRBs, who desire more specific and detailed guidance. If IRBs, PIs, and sponsors are willing to act in good faith to make a genuine effort to interpret the criteria and apply them to a given study, and take the necessary time to plan and conduct community consultation and public disclosure, then it is certainly possible to use the criteria well to do a good job. However, because use of the emergency research regulations is relatively rare, most investigators, sponsors, and IRBs lack experience with them. Thus, clarification is warranted and will be helpful.

(2) How should specific criteria be clarified?

(a) The key criteria of "unproven or unsatisfactory" undoubtedly need clarification. In particular, "unsatisfactory" was shown in the PolyHeme trial to be both misunderstood and contested. In my view, "unsatisfactory", in order to justify proceeding without consent, should be a stringent criterion. It should NOT be synonymous with "imperfect", as Northfield Laboratories, some IRBs, and some commentators have asserted. Such a broad definition would obviate the need for consent altogether, since no treatment is perfect. Similarly, the assertion that equipoise regarding the adequacy of an experimental treatment in comparison with a standard treatment is sufficient to support emergency research would obviate consent in research.

Instead, the argument that a treatment is "unsatisfactory" should be supported with clear evidence of inadequacy with respect to the desired end. In emergent circumstances, the very reason for considering waived-consent research is that there is nothing that really works well at all, and research, rather than improvisation, is needed in order to make progress in treatment. Mere imperfection is not sufficient grounds for waiving consent, even in emergencies.

Although the term "unsatisfactory" is difficult to define precisely, and can only be meaningfully applied in the context of the particular circumstances and interventions under consideration, FDA and IRBs should require investigators and sponsors to make

the case that there is a meaningful failure of current treatment to achieve a desired end; more is at stake than mere improvement.

I recognize the possibility that FDA might choose to equate "unproven or unsatisfactory" with the existence of clinical equipoise – that is, simply with the statement of a valid research question. I urge very strongly that if FDA takes this route, the determination should not be disguised as a clarification. Instead, the "unproven or unsatisfactory" criteria should be removed from the regulations, as fundamentally unnecessary. Directly amending the regulations in this way would in such a case promote transparency of process and require broader public attention and comment than undercutting the regulations by defining away precisely that criterion which most properly justifies waived-consent research.

(b) "prospect of direct benefit" – The challenge here is NOT to ensure that everyone is convinced that subjects randomized to the experimental intervention are likely to benefit from it. Such a perspective is untenable in the research context, and serves only to promote confusion between research and treatment. Instead, FDA and IRBs should focus on the nature, quality, extent and findings of prior trials of the experimental intervention. In order for an experimental intervention to hold out a meaningful prospect of direct benefit in the context of emergency research, the body of evidence supporting the proposed phase III study must be robust.

Difficulty in applying this criterion is not by any means unique to emergency research; it is pervasive in clinical research. However, the challenges of the concept arise differently in different research contexts, and as the PolyHeme trial has shown, the emergency research context has raised concerns about tradeoffs between the urgency of the problem that a waiver trial proposes to address and the quality and quantity of the evidence assembled to justify the trial itself. IRBs are not always as vigilant as they should be in requiring investigators and sponsors to explain why a given design is necessary at a given time. FDA should provide more guidance to support this assessment.

(c) "practicability" -- in this context, determining that research is "impracticable" without the emergency consent waiver should mean that as much information as possible has been gleaned through prior research, and no further meaningful information can be reasonably gathered without the waiver. It should NOT mean only that research can proceed more quickly by using the waiver.

(5) What are the costs, benefits, and feasibility of community consultation?
Community consultation, when done well, necessarily takes time, effort, commitment, and investment, from investigator, sponsor, and IRB. It is essential that community consultation be understood as genuine interaction and an opportunity for public discourse. It should be an exchange, not a rhetorical or public relations exercise. Arguments that public meetings are not effective because nobody attends should be viewed as proof that the relevant communities have not been contacted – not as proof that the proposed research is accepted by all.

(6) What aspects of community consultation are effective mechanisms for human subject protection? Attempts to provide and exchange clear information and to model debate about the pros and cons of emergency waived-consent research are most likely to promote useful community reflection and feedback. Reaching the relevant communities is best accomplished through existing organizations and community leaders, and using advisory board and focus group mechanisms can help to ensure that genuine exchange is promoted and that venues for reaching community members are identified and utilized. Real humility on the part of investigators and sponsors, and the real desire to explain and teach about research rather than simply to "sell" it or get it done, are the best ways to promote community involvement and response. All of this is becoming recognized as the scholarly literature on community consultation grows.

(7) Are there elements of community consultation, both procedural and substantive, that should, at a minimum, be required? Unfortunately, attempting to set minimal requirements are problematic because of the need to address each study on an individual basis and in context. Similarly, setting minimal requirements raise the prospect of "cookbook" emergency research, which must at all costs be avoided. Individually considering a given study in context takes work; it is understandable but troubling that investigators and sponsors would prefer a rote checklist to careful planning.

It would, however, be easy to require that sponsors and investigators considering emergency research contact the IRB well in advance of protocol submission, and that the IRB work with the investigator to identify one or more IRB members, faculty members, and/or community advisors to assist the investigator in preparing to do community consultation. This enables investigators and IRBs to identify and apply the community consultation requirement in a manner specific to particular research. UNC School of Medicine has informally followed such a plan since 1996.

Another minimal requirement that should be easy to institute, and is absolutely necessary, is that information about the study, both when proposed and after IRB approval, MUST be readily available to individuals who seek it at any time during the community consultation process and during the study itself. This means wide promulgation of materials, website information, telephone numbers to call to reach the IRB, a study coordinator, or information clearinghouse, etc. Surprisingly, this does not seem to be considered important by some IRBs – or else they fail to realize how much information saturation is necessary. The PolyHeme trial again provides an example of how difficult some study sites made it to find even information about the trial.

(8) Would opt-out mechanisms provide a necessary protection? Yes, opt-out mechanisms are necessary but far from sufficient to protect subjects. When opt-out mechanisms are used, several factors are key. First, the availability of an opt-out mechanism should not be conflated with the ability to raise questions and request study design changes; this all-too-common conflation runs the risk of conveying the message, "If you don't like the study, you can opt out", thus discouraging communities from suggesting or requesting changes in design or implementation, or from rejecting the study entirely. Second, knowledge of the study must be widespread for opt-out mechanisms to be meaningful. Community consultation does not require that everyone in the community participate, but for an opt-out mechanism to be meaningful it must be

available to everyone in the relevant communities. In addition, information about the start and end dates of study enrollment must be well-promulgated in order for individuals to make use of the opt-out mechanism. Multiple mechanisms may be needed, and may vary with study design. For example, wearing an opt-out bracelet is only suitable for a study of short duration. However, the use of opt-out databases for longer-term studies raises questions of confidentiality, data security, accuracy and updating, and certainty of access.

(9) Who should use the information obtained from the community consultation, and how should they use it? As with question 7, although the desire for standardization and specificity is understandable, it is quite problematic to specify how the information obtained through community consultation should be used. Specificity poses the risk of reducing community conversation to a telephone poll with specified percentages of responses and a 'passing score'. This kind of rote regulatory requirement cannot replace real reflection by the IRB, the investigator, and the community.

Although this may sound paradoxical and overly vague, in my view the investigator and sponsor should continually ask themselves and their community advisors the question "Are we done yet?" – and they should not expect to come upon a clear answer. Instead, the PROCESS of working with communities should be one that promotes reflection about the question, and ultimately a sense of 'approximate closure' should govern the decision that the community consultation process has formally ended – with provision made, of course, to continue to solicit and receive community input THROUGHOUT THE DURATION OF THE STUDY.

(10) Are there others besides the IRB who should play a role in determining the adequacy of the plan for community consultation and the material to be publicly disclosed? This is a surprising question. OF COURSE the IRB should consult with all the listed "others"(sponsors, investigators, community leaders, advisory committees, ethics scholars, etc) in the process of determining the adequacy of a community consultation plan, even if the IRB has the ultimate approval authority.

(11) Community meetings requirements:
(a) Should the regulations require documentation? YES, it should be required!! Regarding whose responsibility this is, from a regulatory standpoint, the sponsor is the logical candidate because the FDA's relationship is with the sponsor. However, both the sponsor and the investigator are often strongly motivated to characterize community consultation in ways that serve their own interests. For that reason, the IRB or an independent observer functioning at the behest of the IRB should document the relevant activities. The costs of this documentation process should be borne by the sponsor.

(b) Should this documentation be submitted to FDA? Yes, if FDA is going to play a more meaningful role in the implementation of the waiver rule, then documentation of community consultation should be required. Posting to the public docket makes sense, though it would be helpful if FDA could make the public docket more user-friendly; it is not all that easy to access.

(c) Should this documentation be available elsewhere, for example on clinicaltrials.gov? Yes, documentation should be readily available, and the FDA docket is difficult to access and search. clinicaltrials.gov, and/or the website of the sponsor or of individual IRBs, would be appropriate additional venues. clinicaltrials.gov in particular seems a logical and easy-to-use location.

(**12) Should some minimal information (e.g., AE reports, protocol, informed consent document) be required to be publicly disclosed to study communities?** YES OF COURSE, the study protocol, informed consent documents, published reports of prior research, investigator's brochure, and adverse events should all, at a minimum, be available and publicly disclosed to the relevant communities. Draft materials should be shared with the communities as part of the community consultation process BEFORE IRB approval of the research. Final materials should then be made available after the research has been approved. THIS INFORMATION SHOULD BE MADE PUBLIC REGARDLESS OF SPONSORS' CLAIMS THAT IT IS CONFIDENTIAL. In this context, commercial confidentiality and trade secrets are incompatible with community consultation and public disclosure, and preservation of confidentiality completely undercuts discussion and information exchange.

(13) Should the full protocol, investigator's brochure, etc. be available to the general public before initiation of the clinical investigation? YES, this information should also be made available via the public docket, clinicaltrials.gov, the sponsor's or IRB's website, or other public sites – for ALL emergency research, regardless of the sponsor's claims of commercial confidentiality or trade secrets. It is important to recognize the many instances in which expansive sponsor claims of confidentiality are attempted, but ultimately fail. A key example is provided by the experience of sponsors and investigators participating in Gene Transfer Safety Symposia after adverse events in gene transfer research. Information-sharing in these forums is routinely resisted at first, and uniformly valued later.

(14-17) These questions relate to public disclosure of information after the completion of the clinical investigation. These urgent and important questions are probably not significantly different for emergency research than they are for other research, although the commitment to communities is heightened in emergency research. The resistance to prompt publication of results, regardless of their nature or quality, should be comprehensively addressed by FDA and others.

(18-19) Is additional public discussion important? Additional review would in many cases be helpful, especially for multicenter studies, to assist IRBs in considering the questions held in common across study sites. However, when IRBs approach their task thoughtfully, many if not most of the important questions in emergency research are site-specific. Additional review might then be local. For example, in North Carolina, in order to permit emergency research to go forward, state regulations had to be amended to permit human subjects research to go forward without consent in specific circumstances. In the case of emergency waived-consent research, investigators are required to submit notice of the proposed study and community consultation information to the state

Medical Care Commission, which reviews the information and can schedule a public meeting as an additional consultation mechanism. [See 10A North Carolina Administrative Code 13B .3302(j).] Such an additional review mechanism at the state level could take advantage of the availability of local relevant scientific and/or research ethics expertise on a case-by-case basis.

(20-21) Are there any additional challenges to the conduct of emergency research that have not been identified by the preceding questions? What are they and how should they be addressed? The PolyHeme trial raised several important questions that merit additional consideration. These include: (1) the meaning of a Special Protocol Assessment and its relationship to the IRB review process and the process of community consultation; (2) the notification requirement when an IRB "cannot approve" a waived-consent trial, and ensuring that investigators and sponsors are not able to evade that requirement; (3) ensuring that the statistical design of a waived-consent trial be sufficient to show that a test article is <u>superior</u> to a treatment deemed "unsatisfactory", since a noninferiority design can show only that a test article is no worse than an unsatisfactory standard treatment – a determination inadequate to justify the use of the waiver rule; (4) ensuring that the communities of potential subjects are drawn from communities capable of benefiting from the test article if approved for use – which seems far from certain in the case of PolyHeme, which has little application in the urban trauma settings where it was studied; and (5) the overall view, held by too many sponsors and investigators, that research regulation is a barrier to progress, rather than an opportunity to work together in good faith to improve research and protect human subjects. Rather than addressing these considerations in detail, I will refer to two published articles on the emergency waiver rule as applied to PolyHeme trial, which addresses these questions in more detail:

> Kipnis, K., King, N. M. P., and Nelson, R. M.: Trials and Errors: An Open Letter to IRBs Considering Northfield Laboratories' PolyHeme Trial. *American Journal of Bioethics*. 2006; 6(3):1-4.
>
> Kipnis, K., King, N. M. P., and Nelson, R. M.: Trials and Errors: Barriers to Oversight of Emergency Research. *IRB: Ethics & Human Research.* 2006;28(2:16-19, 2006.

In closing, I commend the FDA for holding the Part 15 hearing and for soliciting comments on both the hearing questions and the revised guidance document on emergency research. I very much hope that FDA's response to the materials submitted will be timely, comprehensive, and thoughtful. Thank you for your attention to these extremely important matters.